

Nanoparticles-Based Cancer Vaccines

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Abstract—An exciting approach to cancer treatment has been offered by the progress in the development of nanoscale drug delivery systems. An exceptional characteristic of these nanosystems lies in their capacity to stimulate the immune system, which could be the foundation for the design of a cancer vaccine. The current mini-review focuses on the role that the nanoparticles may play as anticancer immunizers.

Keywords — cancer vaccine, nanoparticles, immunity

A new and exciting approach to cancer treatment has been offered by the progress in nanoscale drug delivery systems.[1, 2] The greatest objective of the use of these nanoscale drug systems is to simultaneously deliver high doses of active bionanomolecules at specific sites and to reduce systemic toxicity.[3] Some of the current clinical experiments imply that nanostructured cytostatics, such as doxorubicin encapsulated in liposomes (Doxil®) and paclitaxel bound to nanoparticles (Abraxane®)[4] could extend survival in advanced cancers. A very important characteristic of these nano-biosystems lies in their capacity to enhance the immune system, which could be the foundation for the design of a cancer vaccine.[5] Even if such drug delivery systems represent potential future cancer prevention strategies, the development of a true anticancer vaccine still remains elusive. Inert nanobeads, recombinant virus-like particles and immunostimulating complexes are being employed in cancer vaccine research as they are efficient enough to generate both cellular and humoral immune reactions.[6] There have been comprehensive research of the use of nanoparticles as pharmaceutical drug carriers enhancing therapeutic agent potency with many of these carriers being successfully developed until now.[7-9]. The main cargo of nanocarriers in tumor immunotherapy are usually peptides or DNA encoding tumor-associated antigens (TAAs). TAAs are abnormal proteins aberrantly expressed by tumor cells, but which don't normally appear in normal tissues. Nowadays, most tumors are assumed to express TAAs, this being proved by multiple animal tumor reviews. The immune system can be activated to detect these TAAs as non- self, thus affecting specific

anti-tumor responses. Immunotherapeutically, there is a dire need for novel TAA carriers that might both actively or passively target professional APCs, known as dendritic cells (DCs), thus generating a powerful tumor-specific cytotoxic CD8+ T lymphocyte (CTL) response. The particular importance of DC targeting and activation is given by the fact that DCs are strong generators of immune responses. Achieving an effective anti-tumor CTL response requires the activation of DCs in order to produce a pro-inflammatory (Th1) reaction. This reaction triggers IFN- gamma producing T lymphocytes. Subsequently, nanocarriers can be created in such a way as to target the tumor itself, generating a site-specific concentration of TAAs and/or adjuvants, with a controlled delivery for the development of long-term antigenic memory. The physico-chemical properties and their versatility which helps improve tumor targetability make nanoscale carriers able to meet all the above mentioned objectives.[10], [11]. These nanocarriers bring more benefits than the infusion of the soluble form of the antigen, such as: 1) drug/antigen/adjuvant protection from premature enzymatic and proteolytic degradation, 2) improved drug/antigen/adjuvant absorption into targeted tumor tissue by the EPR impact or by active ligand-based targeting, and 3) capacity to control the pharmacokinetic and drug/antigen/adjuvant tissue distribution profile and to improve cellular assimilation by DCs, generating a powerful immunostimulatory cascade[12]. Moreover, these nanocarriers are superior due to multi-component loading which is of great importance mainly in immunotherapy, where there is strong requirement for simultaneous release of antigens, immunoadjuvants and targeting ligands.[3][13][14]. The large surface area of nanoscale carriers also eases surface functionalization. Their small size allows for a broad surface/volume ratio, therefore enhancing the efficacy of reaction kinetics and multiple surface chemical conversions. The manufacture of these multifunctional nanoscale carriers with controlled features often calls for the attachment of proteins, peptides, polymers, cell-penetrating moieties, reporter groups and other functional and targeting ligands to the carrier surface. This simple change mostly proceeds by means of a non-covalent hydrophobic communication or via covalent conjugation of proteins and peptides onto the nanocarrier's surface.[14] Therefore, the simple design and use of nanoparticles associated with their multifunctionality turns them into adjustable and appealing carrier systems for tumor vaccines and immunotherapy.

We were able to demonstrate that combined administration of both embryonic stem cells (ESC) and multi-walled carbon nanotubes can rebuild antitumor immunity in tumor animal models.[15] Following the administration of a nano-biosystem composed of MWCNTs and of embryonic stem cells, the

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kinetics of tumor growth in a MC 38 xenograft colon cancer model was closely monitored. Importantly, after the treatment, the volumetric evolution of tumors revealed that, as compared to ESC, MWCNTs and control group, the area under curve (AUC) corresponding to ESC+MWCNTs group was significantly lower. Moreover, in the ESC and MWCNTs group, the tumor-growing rate was also significantly lower compared to control group. T rejected tumor masses from propagation and development compared with the other groups.. Data suggest that MWCNT administration in mice strongly enhances production of INF- γ and TNF-secreting CD8+ T cells, unlike physiological saline solution or ESC administration alone. The experiments also revealed that apoptosis of tumor cells in the ESC+MWCNTs vaccine group is significantly higher from that of the control group and marginally significant to ESC or MWCNTs groups. These results suggest that immunization with MWCNTs and ESC could lead to significant protection against cancer development. It has been shown that ESC cells suppress cancer growth by CD8+T and CD4+T cells activation.

References

- [1] Huang M, Lin S, Hsiao C, Chao H, Yang H, Liao C et al. Emulsified nanoparticles containing inactivated influenza virus and CpG oligodeoxynucleotides critically influences the host immune responses in mice. *PLoS One* 2010; 5:e12279.
- [2] Iancu ,Cornel, Ilie I,R., Georgescu C,E., Ilie ,Razvan, Biris A,R., Mocan ,Teodora et al. Applications of Nanomaterials in Cell Stem Therapies and the Onset of Nanomedicine.
- [3] Krishnamachari Y, Geary SM, Lemke CD, Salem AK. Nanoparticle delivery systems in cancer vaccines. *Pharm Res* 2011; 28:215-236.
- [4] Ge W, Li Y, Li Z, Zhang S, Sun Y, Hu P et al. The antitumor immune responses induced by nanoemulsion-encapsulated MAGE1-HSP70/SEA complex protein vaccine following peroral administration route. *Cancer immunology, immunotherapy* 2009; 58:201-208.
- [5] Sun Y, Sui Y, Wu D, GE W, YE J, ZHANG X. Preparation of nanoemulsion-encapsulated tumor specific antigen and study on its character and antitumor immunity. *Chin Pharmacol Bull* 2005; 21:288-291.
- [6] Jain S, Khomane K, K Jain A, Dani P. Nanocarriers for transmucosal vaccine delivery. *Current Nanoscience* 2011; 7:160-177.
- [7] Shi R, Hong L, Wu D, Ning X, Chen Y, Lin T et al. Research Paper Enhanced Immune Response to Gastric Cancer Specific Antigen Peptide by Coencapsulation with CpG Oligodeoxynucleotides in Nanoemulsion. *Cancer biology & therapy* 2005; 4:218-224.
- [8] Wu K, Nie Y, Guo C, Chen Y, Ding J, Fan D. Molecular basis of therapeutic approaches to gastric cancer. *J Gastroenterol Hepatol* 2009; 24:37-41.
- [9] Akagi T, Baba M, Akashi M. Biodegradable nanoparticles as vaccine adjuvants and delivery systems: regulation of immune responses by nanoparticle-based vaccine. In: *Anonymous Polymers in Nanomedicine*: Springer; 2012. p. 31-64.
- [10] Jabbari E. Targeted delivery with peptidomimetic conjugated self-assembled nanoparticles. *Pharm Res* 2009; 26:612-630.
- [11] Zhang Z, Tongchusak S, Mizukami Y, Kang YJ, Ioji T, Touma M et al. Induction of anti-tumor cytotoxic T cell responses through PLGA-nanoparticle mediated antigen delivery. *Biomaterials* 2011; 32:3666-3678.
- [12] Krishnamachari Y, Geary SM, Lemke CD, Salem AK. Nanoparticle delivery systems in cancer vaccines. *Pharm Res* 2011; 28:215-236.
- [13] Krishnamachari Y, Geary SM, Lemke CD, Salem AK. Nanoparticle delivery systems in cancer vaccines. *Pharm Res* 2011; 28:215-236.
- [14] Uhl M, Aulwurm S, Wischhusen J, Weiler M, Ma JY, Almirez R et al. SD-208, a novel transforming growth factor beta receptor I kinase inhibitor, inhibits growth and invasiveness and enhances immunogenicity of murine and human glioma cells in vitro and in vivo. *Cancer Res* 2004; 64:7954-7961.
- [15] Mocan T, Iancu C. Effective colon cancer prophylaxis in mice using embryonic stem cells and carbon nanotubes. *International Journal of Nanomedicine* 2011; 6:1945.